Electrochemical synthesis and studies of substituted 2-thiopyridines

E. A. Kaigorodova,[a] *L. D. Konyushkin,*[b]* *M. E. Niyazymbetov,*[b]
S. N. Kvak,[b] *V. N. Zaplishny,*[a] *and V. P. Litvinov*[b]

[a]*Kuban' State Agricultural University,*
13 ul. Kalinina, 350044 Krasnodar, Russian Federation
[b]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,*
47 Leninsky prosp., 117913 Moscow, Russian Federation.
Fax: +7 (095) 135 5328

A series of substituted 2-alkyl(aryl-, hetaryl-)thiopyridines was prepared by cathodic electrolysis of thiols in the presence of 2-chloro-3-cyano-4-methoxymethyl-6-methylpyridine or 4-chloro-6-methyl-3-oxo-1*H*-furo[3,4-*c*]pyridine. The reaction of 3-cyano-4-methoxymethyl-6-methyl-2(1*H*)-thiopyridone with alkyl halides in the presence of KOH is regioselective and leads to *S*-alkyl derivatives. The advantages of electrosynthesis for the preparation of 2-alkylthiopyridines fused with 2(5*H*)-furanone and of 3-aminothieno[2,3-*b*]pyridines is demonstrated.

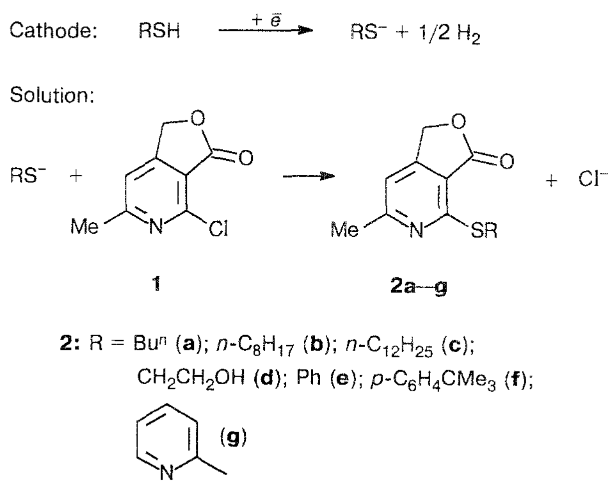
Key words: electrosynthesis; alkylation; 2(1*H*)-thiopyridone; thieno[2,3-*b*]pyridine; disulfide.

2-Alkyl(aryl-, hetaryl-)thiopyridines are of interest as potential biologically active compounds and synthons for fine organic synthesis.[1] The known routes for the preparation of these compounds are based on alkylation of 2(1*H*)-thiopyridones with halogen derivatives or the reaction of 2-halopyridines with thiols.[2] The latter pathway usually involves the formation of salts of thiols under the action of alkaline metals or bases, the excess of which is not always desirable. It has been shown recently that some functionally substituted sulfides can be prepared using electrolysis.[3]

In the present work we synthesized and studied hitherto unknown pyridine sulfides annelated with a lactone ring. Since these compounds are unstable in an alkaline medium, the conventional method, *viz.* thioalkylation of halopyridine, was unacceptable. Therefore, the electrochemical method was chosen to prepare thiopyridines fused with 2(5*H*)-furanones.

Cathodic electrolysis of thiols in the presence of chloropyridine **1** was carried out at a Pt electrode in a 0.3 *N* solution of Et_4NBr in abs. MeCN. The thiolate anion[3] generated at the cathode reacts with **1** (Scheme 1) to afford sulfides (**2a—g**) in high yields (Table 1).

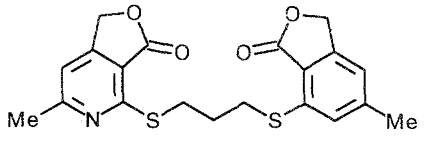
Scheme 1



1 **2a—g**

2: R = Buⁿ (**a**); *n*-C_8H_{17} (**b**); *n*-$C_{12}H_{25}$ (**c**); CH_2CH_2OH (**d**); Ph (**e**); *p*-$C_6H_4CMe_3$ (**f**); (**g**)

The electrolysis was carried out in a diaphragm cell at 20—25 °C in an atmosphere of argon by passing no more than 1.05—1.10 F mol^{-1} of electricity under galvanostatic conditions. In conformity with the literature data,[4] the high reactivity of the thiolate anions was ensured by using an aprotic solvent, MeCN, and a salt having a low tendency to form ion pairs (Et_4NBr) as the supporting electrolyte. The electrolysis of 1,3-propanedithiol in the presence of chloropyridine **1** at the molar ratio 1 : 2 and with 2 equiv. of electricity gives disulfide **3** in 35 % yield (see Table 1).



3

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2215—2219, December, 1994.

Table 1. Yields and physicochemical properties of the compounds synthesized

Compound	Yield (%)	M.p. /°C	^{1}H NMR (δ, *J*/Hz)	Found/Calculated (%)				Molecular formula
				C	H	N	S	
2a	75	88—89 (from hexane)	0.93 (t, 3 H, Me, *J* = 7.0); 1.20—1.90 (m, 4 H, 2 CH_2); 2.56 (s, 3 H, Me); 3.27 (t, 2 H, CH_2S, *J* = 7.0); 5.17 (s, 2 H, CH_2O); 6.9 (s, 1 H, CH)	60.68 60.73	6.30 6.37	5.80 5.90	13.36 13.51	$C_{12}H_{15}NO_2S$
2b	74	82—83 (from hexane)	0.85 (t, 3 H, Me, *J* = 7.0); 1.25—1.68 (m, 12 H, 6 CH_2); 2.55 (s, 3 H, Me); 3.25 (t, 2 H, CH_2S, *J* = 6.8); 5.33 (s, 2 H, CH_2O); 7.20 (s, 1 H, CH)	65.70 65.49	7.85 7.90	4.47 4.77	10.98 10.93	$C_{16}H_{23}NO_2S$
2c	75	89—89.5 (from hexane)	0.87 (t, 3 H, Me, *J* = 4.5); 1.1—1.8 (m, 20 H, 10 CH_2); 2.60 (s, 3 H, Me); 3.28 (t, 2 H, CH_2S, *J* = 6.9); 5.19 (s, 2 H, CH_2O); 6.90 (s, 1 H, CH)	68.68 68.72	8.96 8.94	4.00 4.01	8.99 9.17	$C_{20}H_{31}NO_2S$
2d	91	54—55 (from hexane)	2.57 (s, 3 H, Me); 3.45 (t, 2 H, CH_2S, *J* = 6.0); 3.58 (br.s, 1 H, OH); 3.93 (t, 2 H, CH_2OH, *J* = 5.5); 5.18 (s, 2 H, CH_2O); 6.95 (s, 1 H, CH)	53.26 53.32	4.87 4.92	6.18 6.22	14.41 14.23	$C_{10}H_{11}NO_3S$
2e	83	166—167 (from MeCN)	2.33 (s, 3 H, Me); 5.15 (s, 2 H, CH_2O); 6.85 (s, 1 H, CH); 7.38 (m, 5 H, Ph)	65.40 65.35	4.30 4.31	5.29 5.44	12.38 12.46	$C_{14}H_{11}NO_2S$
2f	73	181—182 (from MeCN)	1.30 (s, 9 H, 3 Me); 2.37 (s, 3 H, Me); 5.15 (s, 2 H, CH_2O); 6.85 (s, 1 H, CH); 7.81 (m, 4 H, C_6H_4)	68.89 68.98	6.01 6.11	4.41 4.47	10.23 10.23	$C_{18}H_{19}NO_2S$
2g	69	167—169 (from MeCN)	2.40 (s, 3 H, Me); 5.17 (s, 2 H, CH_2O); 6.80—7.50 (m, 4 H, 4 CH); 8.54 (d.d, 1 H, H-5, *J* = 1.25)	60.38 60.45	3.70 3.90	10.69 10.85	12.36 12.41	$C_{13}H_{10}N_2O_2S$
3	35	164—165	2.32 (m, 2 H, CH_2); 2.55 (s, 6 H, 2 Me); 3.49 (t, 4 H, 2 CH_2S, *J* = 7.0); 5.3 (s, 4 H, 2 CH_2O); 7.16 (s, 2 H, 2 CH)	56.59 56.70	4.51 4.51	6.90 6.96	15.83 15.90	$C_{19}H_{18}N_2O_4S_2$
5	92	232.5—234.5 (from BuOH)	2.55 (s, 3 H, Me); 3.39 (s, 3 H, OMe); 4.48 (s, 2 H, CH_2O); 6.77 (s, 1 H, CH); 12.80 (br.s, 1 H, NH)	55.59 55.65	5.10 5.19	14.27 14.42	16.39 16.51	$C_9H_{10}N_2OS$
6a	93	63—64 (from EtOH)	2.57 (s, 3 H, Me); 2.62 (s, 3 H, SMe); 3.46 (s, 2 H, CH_2O); 7.17 (s, 1 H, CH)	57.63 57.67	5.60 5.81	13.38 13.45	15.20 15.39	$C_{10}H_{12}N_2OS$
6b	84	82—83 (from EtOH)	1.04 (t, 3 H, Me, *J* = 6.5); 1.75 (m, 2 H, CH_2); 2.56 (s, 3 H, Me); 3.28 (t, 2 H, CH_2S, *J* = 7.0); 3.46 (s, 3 H, OMe); 4.56 (s, 2 H, CH_2O); 7.18 (s, 1 H, CH)	60.88 60.99	6.78 6.82	11.54 11.85	13.48 13.57	$C_{12}H_{16}N_2OS$
6c	66* 77**	Oil	0.96 (t, 3 H, Me, *J* = 7.0); 1.46—1.70 (m, 4 H, 2 CH_2); 2.55 (s, 3 H, Me); 3.28 (t, 2 H, CH_2S, *J* = 7.0); 3.46 (s, 3 H, OMe); 4.53 (s, 2 H, CH_2O); 7.13 (s, 1 H, CH)	62.35 62.37	7.20 7.25	11.12 11.19	12.62 12.81	$C_{13}H_{18}N_2OS$
6d	98	51—52 (from EtOH)	2.57 (s, 3 H, Me); 3.45 (s, 3 H, OMe); 3.97 (d, 2 H, CH_2S, *J* = 4.8); 4.56 (s, 2 H, CH_2O); 5.09—5.39 (d.d.d, 2 H, $=CH_2$, *J* = 15, *J* = 11, *J* = 1.5); 5.92—6.06 (m, 1 H, $H_2CC\underline{H}{=}CH_2$); 7.19 (s, 1 H, CH)	61.34 61.51	6.20 6.02	11.89 11.95	13.66 13.68	$C_{12}H_{14}N_2OS$
6e	95	111—113 (from EtOH)	2.55 (s, 3 H, Me); 3.46 (s, 3 H, OMe); 4.12 (s, 2 H, CH_2); 4.58 (s, 2 H, CH_2O); 7.21 (s, 1 H, CH)	52.34 52.37	4.70 4.79	11.11 11.10	12.52 12.71	$C_{11}H_{12}N_2O_3S$
6f	91	48—49 (from EtOAc—hexane, 1 : 1)	1.29 (t, 3 H, Me, *J* = 7.1); 2.52 (s, 3 H, Me); 3.49 (s, 3 H, CH_2OMe); 4.01 (s, CH_2S); 4.22 (q, 2 H, CH_2Me, *J* = 7.1); 4.56 (s, 2 H, H-3, $COCH_2$); 7.10 (s, 1 H, CH)	55.62 55.70	5.70 5.75	9.79 9.99	11.44 11.44	$C_{13}H_{16}N_2O_3S$

Table 1. (Continued)

Compound	Yield (%)	M.p. /°C	^{1}H NMR (δ, *J*/Hz)	Found/Calculated (%) C	H	N	S	Molecular formula
6g	31* 70**	47.5—48 (from hexane)	2.47 (s, 3 H, Me); 3.47 (s, 3 H, OMe); 4.60 (s, 2 H, CH_2O); 7.27—7.59 (m, 4 H, 4 CH); 8.47 (d.d.d, 1 H, CH, $^4J_{H-6, H-4}$ = 2.0, $^5J_{H-6, H-3}$ = 1.0, $^3J_{H-6, H-5}$ = 4.0)	61.73 61.97	4.80 4.82	15.65 15.49	12.00 11.82	$C_{14}H_{13}N_3OS$
7	38	69—70 (from Me_2CO—hexane, 1 : 1)	2.19 (t, 2 H, CH_2); 2.55 (s, 6 H, 2 Me); 2.70 (t, 4 H, 2 CH_2S, *J* = 7.0); 3.46 (s, 6 H, 2 OMe); 4.56 (s, 4 H, 2 CH_2O); 7.17 (s, 2 H, CH)	58.48 58.85	6.00 5.64	12.98 13.07	14.80 14.96	$C_{21}H_{24}N_4O_2S_2$
8a	63	173—174 (from EtOH)	2.57 (s, 3 H, Me); 3.36 (s, 3 H, OMe); 4.72 (s, CH_2O); 6.89 (br.s, 4 H, Σ NH_2, OH, CH)	52.28 52.37	4.79 4.79	11.01 11.10	12.65 12.71	$C_{11}H_{12}N_2O_3S$
8b	62* 78**	147.5—148.5 (from EtOH)	1.32 (t, 3 H, Me, *J* = 7.2); 2.56 (s, 3 H, Me); 3.41 (s, 3 H, OMe); 4.30 (q, 2 H, CH_2O, *J* = 7.2); 4.82 (s, 2 H, CH_2OMe); 6.92 (br.s, 2 H, NH_2); 7.20 (s, 1 H, CH)	55.62 55.70	5.42 5.75	9.68 69.99	11.35 11.44	$C_{13}H_{16}N_2O_3S$

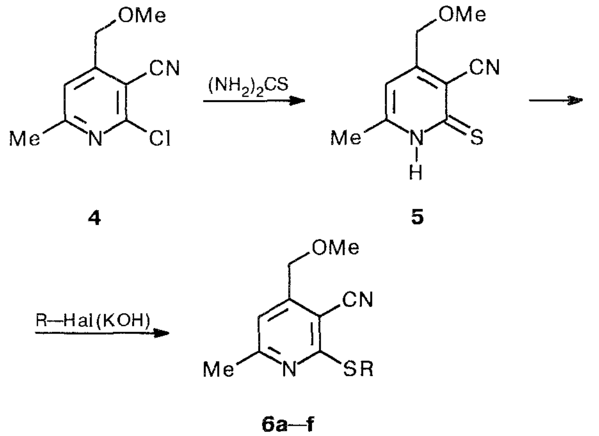
* Compounds prepared by electrochemical synthesis.

** Compounds prepared by chemical synthesis.

The retention of the lactone ring in compounds **2a—g** and **3** is indicated by the presence of ν(C=O) absorption bands at 1750—1720 cm^{-1} and ν(C—O—C) bands at 1140—1025 cm^{-1} in their IR spectra. The ^{1}H NMR spectra of sulfides **2** and **3** are presented in Table 1.

In order to choose the most efficient method for the synthesis of 3-cyano-2-alkylthiopyridines, they were prepared both chemically and by the electrochemical method. Pyridinethione **5** prepared by the reaction of chloropyridine **4** with thiourea by the previously reported method[5] was subjected to alkylation with alkyl halides in ethanol or DMF in the presence of an equimolar amount of KOH (Scheme 2).

Scheme 2



4 **5**

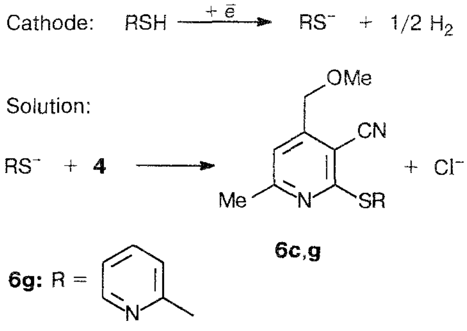
6a—f

6: R = Me (**a**); Pr^n (**b**); Bu^n (**c**); Pr^i (**d**); CH_2COOH (**e**); CH_2COOEt (**f**)

The alkylation occurs regioselectively and gives sulfides **6a—f** in high yields (see Table 1).

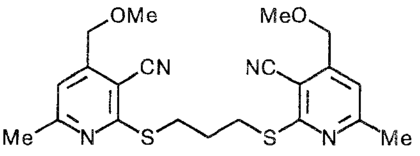
Electrochemical synthesis of 2-alkylthiopyridines was carried out under conditions that have been described above for bicyclic sulfides **2a—g** (Scheme 3).

Scheme 3



6c,g

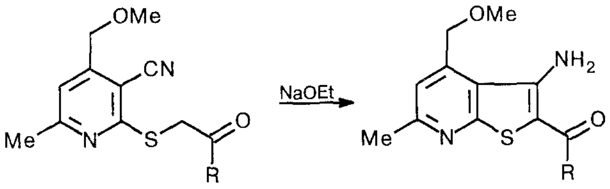
The thiolate anion generated at the cathode reacts with chloropyridine **4** to afford the target products **6c,g**. The cathodic electrolysis of 1,3-propanedithiol in the presence of chloropyridine **4** at the molar ratio 1 : 2 with 2 equivalents of electricity gave sulfide **7** in a 38 % yield.



7

As follows from Table 1, the yields of compounds **6c,g** prepared by alkylation of pyridinethione are considerably higher than those achieved in the electrochemical thioalkylation of chloropyridine, which indicates that side electrochemical processes occur in the latter case.

With compounds **6e,f** as examples we showed the possibility of Thorpe—Ziegler cyclization in the presence of sodium ethoxide in ethanol to yield the corresponding 3-aminothienopyridines (**8a,b**).



6e,f **8a,b**

8: R = OH (**a**); OEt (**b**)

The IR spectra of cyclization products **8a,b** exhibit no ν(C≡N) band. Instead, a number of bands corresponding to the stretching and deformation vibrations of the amino group appear at 3420—3330 cm^{-1}. In the ^{1}H NMR spectra of these compounds, signals for the protons of the amino group appear at δ 6.89—6.92, instead of the signals for the protons of the S—CH_2 group. In addition, (*cf.* Ref. 6) characteristic shifts of the signals for the corresponding protons are observed (see Table 1). It should be noted that in the electrochemical thioalkylation of chloropyridine **4** with ethyl thioglycolate, we isolated not the expected *S*-substituted 3-cyanopyridine **6f**, but the product of its cyclization according to Thorpe—Ziegler **8b** in 62 % yield. This implies that the **6f** produced in the primary reaction, being more reactive (a CH-acid), undergoes further transformation to yield the condensation product under the conditions of galvanostatic electrolysis.

Thus, owing to the mild conditions of the process (the absence of bases, ambient temperature), the electrochemical method of synthesis allows the direct synthesis of 2-thiosubstituted pyridines fused with 2(5*H*)-furanone, which are unstable in an alkaline medium. However, the standard procedure, *viz.*, alkylation of 2(1*H*)-pyridinethiones, is the most suitable for preparing 3-cyano-2-alkylthiopyridines, since the electrochemical synthesis is accompanied by side processes.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ or $(CD_3)_2CO$. IR spectra were obtained on a Specord 75-IR spectrophotometer (for suspensions in vaseline oil). Acetonitrile was dehydrated by multiple distillation from P_2O_5 followed by distillation from K_2CO_3. Et_4NBr was held in a desiccator over P_2O_5. A 0.3 *M* solution of Et_4NBr in MeCN was used as the supporting electrolyte. The variation of the concentrations of reactants during electrolysis and the purity of products were monitored by TLC on Silufol plates (elution was carried out with acetone—hexane mixtures, (1 to 3) : (1 to 5), visualization was carried out by iodine vapor or a solution of $KMnO_4$).

Typical electrolysis was carried out in the following way. 60 mL of a 0.3 *M* solution of Et_4NBr in abs. MeCN containing a mixture of equimolar amounts of a thiol and an organyl halide (0.01 mol) was placed into the cathode section of a cell with a glass diaphragm. 50 mL of a solution of the supporting electrolyte was used as the anolyte. A Pt plate (35 cm^2) was used as the cathode; a Mg rod of diameter 1 cm was used as the anode. The electrolysis was carried out at 20—25 °C under galvanostatic conditions at a current density of 3—5 mA cm^{-2}. The catholyte was stirred with a magnetic stirrer. When 1.05—1.15 F mol^{-1} of electricity had passed, the catholyte was withdrawn, and the solvent was evaporated *in vacuo*. The residue was treated with water, extracted with CH_2Cl_2, and dried with $MgSO_4$. The solvent was evaporated *in vacuo*, and the products were recrystallized from appropriate solvents.

Compounds **3**, **6c,g**, **7**, and **8b** were additionally purified by column chromatography on silica gel (using a (1 to 3) : (1 to 5) acetone—hexane mixture as the eluent).

IR, ν/cm^{-1}: **2a**: 1740, 1570, 1140, 1120; **2b**: 1730, 1575, 1580, 1140, 1050; **2c**: 1730, 1575, 1580, 1140, 1050; **2d**: 3225, 1720, 1625, 1565, 1150, 1060, 1030; **2e**: 3070, 3015, 1750, 1740, 1580, 1570, 1105, 1070, 1020; **2f**: 3070, 3015, 1750, 1590, 1070, 1030, 1025; **2g**: 3075, 3035, 1730, 1590, 1560, 1110, 1080, 1025; **3**: 1720, 1560, 1540, 1110, 1090, 1020; **7**: 2210, 1580, 1540, 1110, 1080, 1050.

3-Cyano-6-methyl-4-methoxymethyl-2(1*H*)-thiopyridone (5). A mixture of 10 mmol of 2-chloro-3-cyano-6-methyl-4-methoxymethylpyridine (**4**) and 10 mmol of thiourea in 20 mL of *n*-butanol was stirred for 4 h at 80 °C. The precipitate was separated, washed with ethanol, and recrystallized from *n*-butanol. IR, ν/cm^{-1}: 2210, 1570, 1195, 1140, 1105.

2-Alkylthio-3-cyano-6-methyl-4-methoxymethylpyridines (6a,g). At 20 °C, a solution of 10 mmol of 3-cyano-6-methyl-4-methoxymethyl-2(1*H*)-thiopyridone (**5**) in 20—25 mL of DMF was mixed with a solution of 10 mmol of alkyl halide and with an equimolar amount of 10 % aqueous KOH. The mixture was kept for 1—3 h and diluted with 5—10 mL of H_2O. The precipitate was filtered off, washed with water, and recrystallized from an appropriate solvent. IR, ν/cm^{-1}: **6a**: 2200, 1530, 1560, 1180, 1115, 1110; **6b**: 2200, 1530, 1570, 1180, 1105, 1095; **6c**: 2200, 1560, 1530, 1170, 1105, 1095; **6d**: 2200, 1560, 1520, 1175, 1110, 1095; **6e**: 2220, 1695, 1570, 1195, 1120, 1100; **6f**: 2200, 1715, 1570, 1530, 1180, 1115, 1095; **6g**: 2220, 1580, 1540, 1100, 1040.

3-Amino-2R-6-methyl-4-methoxymethylthieno[2,3-*b*]pyridines (8). 3.4 mmol of (3-cyano-6-methyl-4-methoxymethyl-2-pyridylthio)acetic acid was added to a solution of EtONa prepared from 7.0 mmol of Na and 20 mL of EtOH. The mixture was boiled for 2 h, cooled, and acidified with 10 % HCl. The precipitate was filtered off and recrystallized from EtOH. IR, ν/cm^{-1}: **8a**: 3390, 3280, 1630, 1580, 1120, 1060; **8b**: 3420, 3330, 1660, 1590, 1550, 1120.

References

1. *Aktual'nye napravleniya issledovaniya i primeneniya khimicheskikh sredstv zashchity rastenii. Khimiya azinov. Itogi nauki i tekhniki. Ser. Organicheskaya khimiya [Modern Trends in the Investigation and Application of Chemical Means for*

Plant Protection. Chemistry of Azines. Division of Organic Chemistry], VINITI, Moscow, 1989, **17**, 72 (in Russian).
2. E. E. Read, *Organic Chemistry of Bivalent Sulfur*, Chem. Publ. Co.INC, 1960, **2**, 106, 110, 125, 126, 338; *ibid*, **3**, 204.
3. M. E. Niyazymbetov, V. A. Petrosyan, L. D. Konyushkin, and V. P. Litvinov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 1605 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1454 (Engl. Transl.)].
4. V. A. Petrosyan, M. E. Niyazymbetov, L. D. Konyushkin, and V. P. Litvinov, *Synthesis*, 1990, 841.
5. A. V. Kadushkin, I. F. Faermark, G. Ya. Shvarts, and V. G. Granik, *Khim.-farm. Zh. [Chem.-Pharm. J.*], 1992, No. 11—12, 62 (in Russian).
6. V. P. Litvinov, Yu. A. Sharanin, L. A. Rodinovskaya, A. M. Shestopalov, V. Yu. Mortikov, and V. K. Promonenkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 2760 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 2528 (Engl. Transl.)].

Received June 24, 1994